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<120> Novel cytochrome P450 monooxygenases and their use for the oxidation of organic substrates

<130> 50915

<140> 10/031,146

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<150> PCT/EP 00/07253

<151> 2000-07-27

<160> 9

<170> Word Perfect version 6.1

<210> 1

<211> 3150

<212> DNA

<213> Bacillus megaterium

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aat tta ccg tta tta aac aca gat aaa ccg gtt caa gct ttg atg aaa 96  
Asn Leu Pro Leu Leu Asn Thr Asp Lys Pro Val Gln Ala Leu Met Lys  
20 25 30

att gcg gat gaa tta gga gaa atc ttt aaa ttc gag gcg cct ggt cgt 144  
Ile Ala Asp Glu Leu Gly Glu Ile Phe Lys Phe Glu Ala Pro Gly Arg  
35 40 45

gta acg cgc tac tta tca agt cag cgt cta att aaa gaa gca tgc gat 192  
Val Thr Arg Tyr Leu Ser Ser Gln Arg Leu Ile Lys Glu Ala Cys Asp  
50 55 60

gaa tca cgc ttt gat aaa aac tta agt caa gcg ctt aaa ttt gta cgt 240  
Glu Ser Arg Phe Asp Lys Asn Leu Ser Gln Ala Leu Lys Phe Val Arg  
65 70 75

gat ttt gca gga gac ggg tta ttt aca agc tgg acg cat gaa aaa aat 288  
Asp Phe Ala Gly Asp Gly Leu Phe Thr Ser Trp Thr His Glu Lys Asn  
80 85 90 95

tgg aaa aaa gcg cat aat atc tta ctt cca agc ttc agt cag cag gca 336  
Trp Lys Lys Ala His Asn Ile Leu Pro Ser Phe Ser Gln Gln Ala

100	105	110	
atg aaa ggc tat cat gcg atg atg gtc gat atc gcc gtg cag ctt gtt Met Lys Gly Tyr His Ala Met Met Val Asp Ile Ala Val Gln Leu Val 115	120	125	384
caa aag tgg gag cgt cta aat gca gat gag cat att gaa gta ccg gaa Gln Lys Trp Glu Arg Leu Asn Ala Asp Glu His Ile Glu Val Pro Glu 130	135	140	432
gac atg aca cgt tta acg ctt gat aca att ggt ctt tgc ggc ttt aac Asp Met Thr Arg Leu Thr Leu Asp Thr Ile Gly Leu Cys Gly Phe Asn 145	150	155	480
tat cgc ttt aac agc ttt tac cga gat cag cct cat cca ttt att aca Tyr Arg Phe Asn Ser Phe Tyr Arg Asp Gln Pro His Pro Phe Ile Thr 160	165	170	528
agt atg gtc cgt gca ctg gat gaa gca atg aac aag ctg cag cga gca Ser Met Val Arg Ala Leu Asp Glu Ala Met Asn Lys Leu Gln Arg Ala 180	185	190	576
aat cca gac gac cca gct tat gat gaa aac aag cgc cag ttt caa gaa Asn Pro Asp Asp Pro Ala Tyr Asp Glu Asn Lys Arg Gln Phe Gln Glu 195	200	205	624
gat atc aag gtg atg aac gac cta gta gat aaa att att gca gat cgc Asp Ile Lys Val Met Asn Asp Leu Val Asp Lys Ile Ile Ala Asp Arg 210	215	220	672
aaa gca agc ggt gaa caa agc gat gat tta tta acg cat atg cta aac Lys Ala Ser Gly Glu Gln Ser Asp Asp Leu Leu Thr His Met Leu Asn 225	230	235	720
gga aaa gat cca gaa acg ggt gag ccg ctt gat gac gag aac att cgc Gly Lys Asp Pro Glu Thr Gly Glu Pro Leu Asp Asp Glu Asn Ile Arg 240	245	250	768
tat caa att att aca ttc tta att gcg gga cac gaa aca aca agt ggt Tyr Gln Ile Ile Thr Phe Leu Ile Ala Gly His Glu Thr Thr Ser Gly 260	265	270	816
ctt tta tca ttt gcg ctg tat ttc tta gtg aaa aat cca cat gta tta Leu Leu Ser Phe Ala Leu Tyr Phe Leu Val Lys Asn Pro His Val Leu 275	280	285	864
caa aaa gca gca gaa gca gca cga gtt cta gta gat cct gtt cca Gln Lys Ala Ala Glu Glu Ala Ala Arg Val Leu Val Asp Pro Val Pro 290	295	300	912
agc tac aaa caa gtc aaa cag ctt aaa tat gtc ggc atg gtc tta aac Ser Tyr Lys Gln Val Lys Gln Leu Lys Tyr Val Gly Met Val Leu Asn 305	310	315	960
gaa gcg ctg cgc tta tgg cca act gct cct gcg ttt tcc cta tat gca Glu Ala Leu Arg Leu Trp Pro Thr Ala Pro Ala Phe Ser Leu Tyr Ala 320	325	330	1008
aaa gaa gat acg gtg ctt gga gga gaa tat cct tta gaa aaa ggc gac 1056			

Lys Glu Asp Thr Val Leu Gly Gly Glu Tyr Pro Leu Glu Lys Gly Asp			
340	345	350	
gaa cta atg gtt ctg att cct cag ctt cac cgt gat aaa aca att tgg			1104
Glu Leu Met Val Leu Ile Pro Gln Leu His Arg Asp Lys Thr Ile Trp			
355	360	365	
gga gac gat gtg gaa gag ttc cgt cca gag cgt ttt gaa aat cca agt			1152
Gly Asp Asp Val Glu Glu Phe Arg Pro Glu Arg Phe Glu Asn Pro Ser			
370	375	380	
gcg att ccg cag cat gcg ttt aaa ccg ttt gga aac ggt cag cgt gcg			1200
Ala Ile Pro Gln His Ala Phe Lys Pro Phe Gly Asn Gly Gln Arg Ala			
385	390	395	
tgt atc ggt cag cag ttc gct ctt cat gaa gca acg ctg gta ctt ggt			1248
Cys Ile Gly Gln Phe Ala Leu His Glu Ala Thr Leu Val Leu Gly			
400	405	410	415
atg atg cta aaa cac ttt gac ttt gaa gat cat aca aac tac gag ctg			1296
Met Met Leu Lys His Phe Asp Phe Glu Asp His Thr Asn Tyr Glu Leu			
420	425	430	
gat att aaa gaa act tta acg tta aaa cct gaa ggc ttt gtg gta aaa			1344
Asp Ile Lys Glu Thr Leu Thr Leu Lys Pro Glu Gly Phe Val Val Lys			
435	440	445	
gca aaa tcg aaa aaa att ccg ctt ggc ggt att cct tca cct agc act			1392
Ala Lys Ser Lys Ile Pro Leu Gly Gly Ile Pro Ser Pro Ser Thr			
450	455	460	
gaa cag tct gct aaa aaa gta cgc aaa aag gca gaa aac gct cat aat			1440
Glu Gln Ser Ala Lys Lys Val Arg Lys Lys Ala Glu Asn Ala His Asn			
465	470	475	
acg ccg ctg ctt gtg cta tac ggt tca aat atg gga aca gct gaa gga			1488
Thr Pro Leu Leu Val Leu Tyr Gly Ser Asn Met Gly Thr Ala Glu Gly			
480	485	490	495
acg gcg cgt gat tta gca gat att gca atg agc aaa gga ttt gca ccg			1536
Thr Ala Arg Asp Leu Ala Asp Ile Ala Met Ser Lys Gly Phe Ala Pro			
500	505	510	
cag gtc gca acg ctt gat tca cac gcc gga aat ctt ccg cgc gaa gga			1584
Gln Val Ala Thr Leu Asp Ser His Ala Gly Asn Leu Pro Arg Glu Gly			
515	520	525	
gct gta tta att gta acg gcg tct tat aac ggt cat ccg cct gat aac			1632
Ala Val Leu Ile Val Thr Ala Ser Tyr Asn Gly His Pro Pro Asp Asn			
530	535	540	
gca aag caa ttt gtc gac tgg tta gac caa gcg tct gct gat gaa gta			1680
Ala Lys Gln Phe Val Asp Trp Leu Asp Gln Ala Ser Ala Asp Glu Val			
545	550	555	
aaa ggc gtt cgc tac tcc gta ttt gga tgc ggc gat aaa aac tgg gct			1728
Lys Gly Val Arg Tyr Ser Val Phe Gly Cys Gly Asp Lys Asn Trp Ala			
560	565	570	575

act acg tat caa aaa gtg cct gct ttt atc gat gaa acg ctt gcc gct		1776
Thr Thr Tyr Gln Lys Val Pro Ala Phe Ile Asp Glu Thr Leu Ala Ala		
580	585	590
aaa ggg gca gaa aac atc gct gac cgc ggt gaa gca gat gca agc gac		1824
Lys Gly Ala Glu Asn Ile Ala Asp Arg Gly Glu Ala Asp Ala Ser Asp		
595	600	605
gac ttt gaa ggc aca tat gaa gaa tgg cgt gaa cat atg tgg agt gac		1872
Asp Phe Glu Gly Thr Tyr Glu Glu Trp Arg Glu His Met Trp Ser Asp		
610	615	620
gta gca gcc tac ttt aac ctc gac att gaa aac agt gaa gat aat aaa		1920
Val Ala Ala Tyr Phe Asn Leu Asp Ile Glu Asn Ser Glu Asp Asn Lys		
625	630	635
tct act ctt tca ctt caa ttt gtc gac agc gcc gcg gat atg ccg ctt		1968
Ser Thr Leu Ser Leu Gln Phe Val Asp Ser Ala Ala Asp Met Pro Leu		
640	645	650
655		
gcg aaa atg cac ggt gcg ttt tca acg aac gtc gta gca agc aaa gaa		2016
Ala Lys Met His Gly Ala Phe Ser Thr Asn Val Val Ala Ser Lys Glu		
660	665	670
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Leu Gln Gln Pro Gly Ser Ala Arg Ser Thr Arg His Leu Glu Ile Glu		
675	680	685
ctt cca aaa gaa gct tct tat caa gaa gga gat cat tta ggt gtt att		2112
Leu Pro Lys Glu Ala Ser Tyr Gln Glu Gly Asp His Leu Gly Val Ile		
690	695	700
cct cgc aac tat gaa gga ata gta aac cgt gta aca gca agg ttc ggc		2160
Pro Arg Asn Tyr Glu Gly Ile Val Asn Arg Val Thr Ala Arg Phe Gly		
705	710	715
cta gat gca tca cag caa atc cgt ctg gaa gca gaa gaa aaa tta		2208
Leu Asp Ala Ser Gln Gln Ile Arg Leu Glu Ala Glu Glu Lys Leu		
720	725	730
735		
gct cat ttg cca ctc gct aaa aca gta tcc gta gaa gag ctt ctg caa		2256
Ala His Leu Pro Leu Ala Lys Thr Val Ser Val Glu Glu Leu Leu Gln		
740	745	750
tac gtg gag ctt caa gat cct gtt acg cgc acg cag ctt cgc gca atg		2304
Tyr Val Glu Leu Gln Asp Pro Val Thr Arg Thr Gln Leu Arg Ala Met		
755	760	765
gct gct aaa acg gtc tgc ccg ccg cat aaa gta gag ctt gaa gcc ttg		2352
Ala Ala Lys Thr Val Cys Pro Pro His Lys Val Glu Leu Glu Ala Leu		
770	775	780
ctt gaa aag caa gcc tac aaa gaa caa gtg ctg gca aaa cgt tta aca		2400
Leu Glu Lys Gln Ala Tyr Lys Glu Gln Val Leu Ala Lys Arg Leu Thr		
785	790	795
atg ctt gaa ctg ctt gaa aaa tac ccg gcg tgt gaa atg aaa ttc agc		2448
Met Leu Glu Leu Leu Glu Lys Tyr Pro Ala Cys Glu Met Lys Phe Ser		
800	805	810
815		

gaa ttt atc gcc ctt ctg cca agc ata cgc ccg cgc tat tac tcg att		2496
Glu Phe Ile Ala Leu Leu Pro Ser Ile Arg Pro Arg Tyr Tyr Ser Ile		
820	825	830
tct tca tca cct cgt gtc gat gaa aaa caa gca agc atc acg gtc agc		2544
Ser Ser Ser Pro Arg Val Asp Glu Lys Gln Ala Ser Ile Thr Val Ser		
835	840	845
gtt gtc tca gga gaa gcg tgg agc gga tat gga gaa tat aaa gga att		2592
Val Val Ser Gly Glu Ala Trp Ser Gly Tyr Gly Glu Tyr Lys Gly Ile		
850	855	860
gcg tcg aac tat ctt gcc gag ctg caa gaa gga gat acg att acg tgc		2640
Ala Ser Asn Tyr Leu Ala Glu Leu Gln Glu Gly Asp Thr Ile Thr Cys		
865	870	875
ttt att tcc aca ccg cag tca gaa ttt acg ctg cca aaa gac cct gaa		2688
Phe Ile Ser Thr Pro Gln Ser Glu Phe Thr Leu Pro Lys Asp Pro Glu		
880	885	890
895		
acg ccg ctt atc atg gtc gga ccg gga aca ggc gtc gcg ccg ttt aga		2736
Thr Pro Leu Ile Met Val Gly Pro Gly Thr Gly Val Ala Pro Phe Arg		
900	905	910
ggc ttt gtg cag gcg cgc aaa cag cta aaa gaa caa gga cag tca ctt		2784
Gly Phe Val Gln Ala Arg Lys Gln Leu Lys Glu Gln Gly Gln Ser Leu		
915	920	925
gga gaa gca cat tta tac ttc ggc tgc cgt tca cct cat gaa gac tat		2832
Gly Glu Ala His Leu Tyr Phe Gly Cys Arg Ser Pro His Glu Asp Tyr		
930	935	940
ctg tat caa gaa gag ctt gaa aac gcc caa agc gaa ggc atc att acg		2880
Leu Tyr Gln Glu Leu Glu Asn Ala Gln Ser Glu Gly Ile Ile Thr		
945	950	955
ctt cat acc gct ttt tct cgc atg cca aat cag ccg aaa aca tac gtt		2928
Leu His Thr Ala Phe Ser Arg Met Pro Asn Gln Pro Lys Thr Tyr Val		
960	965	970
975		
cag cac gta atg gaa caa gac ggc aag aaa ttg att gaa ctt ctt gat		2976
Gln His Val Met Glu Gln Asp Gly Lys Lys Leu Ile Glu Leu Leu Asp		
980	985	990
caa gga gcg cac ttc tat att tgc gga gac gga agc caa atg gca cct		3024
Gln Gly Ala His Phe Tyr Ile Cys Gly Asp Gly Ser Gln Met Ala Pro		
995	1000	1005
gac gtt gaa gca acg ctt atg aaa agc tat gct gac gtt cac caa gtg		3072
Ala Val Glu Ala Thr Leu Met Lys Ser Tyr Ala Asp Val His Gln Val		
1010	1015	1020
agt gaa gca gac gct cgc tta tgg ctg cag cag cta gaa gaa aaa ggc		3120
Ser Glu Ala Asp Ala Arg Leu Trp Leu Gln Gln Leu Glu Glu Lys Gly		
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cga tac gca aaa gac gtg tgg gct ggg taa		3150
Arg Tyr Ala Lys Asp Val Trp Ala Gly		
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Ala Asp Glu Leu Gly Glu Ile Phe Lys Phe Glu Ala Pro Gly Arg Val  
35 40 45

Thr Arg Tyr Leu Ser Ser Gln Arg Leu Ile Lys Glu Ala Cys Asp Glu  
50 55 60

Ser Arg Phe Asp Lys Asn Leu Ser Gln Ala Leu Lys Phe Val Arg Asp  
65 70 75 80

Phe Ala Gly Asp Gly Leu Phe Thr Ser Trp Thr His Glu Lys Asn Trp  
85 90 95

Lys Lys Ala His Asn Ile Leu Leu Pro Ser Phe Ser Gln Gln Ala Met  
100 105 110

Lys Gly Tyr His Ala Met Met Val Asp Ile Ala Val Gln Leu Val Gln  
115 120 125

Lys Trp Glu Arg Leu Asn Ala Asp Glu His Ile Glu Val Pro Glu Asp  
130 135 140

Met Thr Arg Leu Thr Leu Asp Thr Ile Gly Leu Cys Gly Phe Asn Tyr  
145 150 155 160

Arg Phe Asn Ser Phe Tyr Arg Asp Gln Pro His Pro Phe Ile Thr Ser  
165 170 175

Met Val Arg Ala Leu Asp Glu Ala Met Asn Lys Leu Gln Arg Ala Asn  
180 185 190

Pro Asp Asp Pro Ala Tyr Asp Glu Asn Lys Arg Gln Phe Gln Glu Asp  
195 200 205

Ile Lys Val Met Asn Asp Leu Val Asp Lys Ile Ile Ala Asp Arg Lys  
210 215 220

Ala Ser Gly Glu Gln Ser Asp Asp Leu Leu Thr His Met Leu Asn Gly  
225 230 235 240

Lys Asp Pro Glu Thr Gly Glu Pro Leu Asp Asp Glu Asn Ile Arg Tyr  
245 250 255

Gln Ile Ile Thr Phe Leu Ile Ala Gly His Glu Thr Thr Ser Gly Leu  
260 265 270

Leu Ser Phe Ala Leu Tyr Phe Leu Val Lys Asn Pro His Val Leu Gln  
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Lys Ala Ala Glu Glu Ala Ala Arg Val Leu Val Asp Pro Val Pro Ser  
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Tyr Lys Gln Val Lys Gln Leu Lys Tyr Val Gly Met Val Leu Asn Glu  
 305                    310                    315                    320

Ala Leu Arg Leu Trp Pro Thr Ala Pro Ala Phe Ser Leu Tyr Ala Lys  
 325                    330                    335

Glu Asp Thr Val Leu Gly Gly Glu Tyr Pro Leu Glu Lys Gly Asp Glu  
 340                    345                    350

Leu Met Val Leu Ile Pro Gln Leu His Arg Asp Lys Thr Ile Trp Gly  
 355                    360                    365

Asp Asp Val Glu Glu Phe Arg Pro Glu Arg Phe Glu Asn Pro Ser Ala  
 370                    375                    380

Ile Pro Gln His Ala Phe Lys Pro Phe Gly Asn Gly Gln Arg Ala Cys  
 385                    390                    395                    400

Ile Gly Gln Gln Phe Ala Leu His Glu Ala Thr Leu Val Leu Gly Met  
 405                    410                    415

Met Leu Lys His Phe Asp Phe Glu Asp His Thr Asn Tyr Glu Leu Asp  
 420                    425                    430

Ile Lys Glu Thr Leu Thr Leu Lys Pro Glu Gly Phe Val Val Lys Ala  
 435                    440                    445

Lys Ser Lys Lys Ile Pro Leu Gly Gly Ile Pro Ser Pro Ser Thr Glu  
 450                    455                    460

Gln Ser Ala Lys Lys Val Arg Lys Lys Ala Glu Asn Ala His Asn Thr  
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Pro Leu Leu Val Leu Tyr Gly Ser Asn Met Gly Thr Ala Glu Gly Thr  
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Ala Arg Asp Leu Ala Asp Ile Ala Met Ser Lys Gly Phe Ala Pro Gln  
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Val Ala Thr Leu Asp Ser His Ala Gly Asn Leu Pro Arg Glu Gly Ala  
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Val Leu Ile Val Thr Ala Ser Tyr Asn Gly His Pro Pro Asp Asn Ala  
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Lys Gln Phe Val Asp Trp Leu Asp Gln Ala Ser Ala Asp Glu Val Lys  
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Gly Val Arg Tyr Ser Val Phe Gly Cys Gly Asp Lys Asn Trp Ala Thr  
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Thr Tyr Gln Lys Val Pro Ala Phe Ile Asp Glu Thr Leu Ala Ala Lys  
 580                    585                    590

Gly Ala Glu Asn Ile Ala Asp Arg Gly Glu Ala Asp Ala Ser Asp Asp  
 595 600 605

Phe Glu Gly Thr Tyr Glu Glu Trp Arg Glu His Met Trp Ser Asp Val  
 610 615 620

Ala Ala Tyr Phe Asn Leu Asp Ile Glu Asn Ser Glu Asp Asn Lys Ser  
 625 630 635 640

Thr Leu Ser Leu Gln Phe Val Asp Ser Ala Ala Asp Met Pro Leu Ala  
 645 650 655

Lys Met His Gly Ala Phe Ser Thr Asn Val Val Ala Ser Lys Glu Leu  
 660 665 670

Gln Gln Pro Gly Ser Ala Arg Ser Thr Arg His Leu Glu Ile Glu Leu  
 675 680 685

Pro Lys Glu Ala Ser Tyr Gln Glu Gly Asp His Leu Gly Val Ile Pro  
 690 695 700

Arg Asn Tyr Glu Gly Ile Val Asn Arg Val Thr Ala Arg Phe Gly Leu  
 705 710 715 720

Asp Ala Ser Gln Gln Ile Arg Leu Glu Ala Glu Glu Lys Leu Ala  
 725 730 735

His Leu Pro Leu Ala Lys Thr Val Ser Val Glu Glu Leu Gln Tyr  
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Val Glu Leu Gln Asp Pro Val Thr Arg Thr Gln Leu Arg Ala Met Ala  
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Ala Lys Thr Val Cys Pro Pro His Lys Val Glu Leu Glu Ala Leu Leu  
 770 775 780

Glu Lys Gln Ala Tyr Lys Glu Gln Val Leu Ala Lys Arg Leu Thr Met  
 785 790 795 800

Leu Glu Leu Leu Glu Lys Tyr Pro Ala Cys Glu Met Lys Phe Ser Glu  
 805 810 815

Phe Ile Ala Leu Leu Pro Ser Ile Arg Pro Arg Tyr Tyr Ser Ile Ser  
 820 825 830

Ser Ser Pro Arg Val Asp Glu Lys Gln Ala Ser Ile Thr Val Ser Val  
 835 840 845

Val Ser Gly Glu Ala Trp Ser Gly Tyr Gly Glu Tyr Lys Gly Ile Ala  
 850 855 860

Ser Asn Tyr Leu Ala Glu Leu Gln Glu Gly Asp Thr Ile Thr Cys Phe  
 865 870 875 880

Ile Ser Thr Pro Gln Ser Glu Phe Thr Leu Pro Lys Asp Pro Glu Thr  
 885 890 895

Pro Leu Ile Met Val Gly Pro Gly Thr Gly Val Ala Pro Phe Arg Gly

900

905

910

Phe Val Gln Ala Arg Lys Gln Leu Lys Glu Gln Gly Gln Ser Leu Gly  
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Glu Ala His Leu Tyr Phe Gly Cys Arg Ser Pro His Glu Asp Tyr Leu  
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Tyr Gln Glu Glu Leu Glu Asn Ala Gln Ser Glu Gly Ile Ile Thr Leu  
 945                            950                            955                            960

His Thr Ala Phe Ser Arg Met Pro Asn Gln Pro Lys Thr Tyr Val Gln  
 965                            970                            975

His Val Met Glu Gln Asp Gly Lys Lys Leu Ile Glu Leu Leu Asp Gln  
 980                            985                            990

Gly Ala His Phe Tyr Ile Cys Gly Asp Gly Ser Gln Met Ala Pro Ala  
 995                            1000                            1005

Val Glu Ala Thr Leu Met Lys Ser Tyr Ala Asp Val His Gln Val Ser  
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Glu Ala Asp Ala Arg Leu Trp Leu Gln Gln Leu Glu Glu Lys Gly Arg  
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Tyr Ala Lys Asp Val Trp Ala Gly  
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<223> n is g, a, t or c.

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<223> Description of the synthetic sequence: PCR primer

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<210> 4  
<211> 30  
<212> DNA  
<213> Synthetic sequence

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<221> unsure  
<222> 1..30  
<223> n is g, a, t or c.

<223> Description of the synthetic sequence: PCR primer

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<223> n is g, a, t or c.

<223> Description of the synthetic sequence: PCR primer

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gaagcaatga acaagnnca gcgagcaa at ccag

34

<210> 6  
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<212> DNA  
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<223> n is g, a, t or c.

<223> Description of the synthetic sequence: PCR primer

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<210> 7  
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<212> DNA  
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<223> n is g, a, t or c.

<223> Description of the synthetic sequence: PCR primer

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<223> n is g, a, t or c.

<223> Description of the synthetic sequence: PCR primer

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40

&lt;210&gt; 9

&lt;211&gt; 1049

&lt;212&gt; PRT

&lt;213&gt; Bacillus megaterium

&lt;400&gt; 9

Met	Thr	Ile	Lys	Glu	Met	Pro	Gln	Pro	Lys	Thr	Phe	Gly	Glu	Leu	Lys
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Asn	Leu	Pro	Leu	Leu	Asn	Thr	Asp	Lys	Pro	Val	Gln	Ala	Leu	Met	Lys
					20			25					30		

Ile	Ala	Asp	Glu	Leu	Gly	Glu	Ile	Phe	Lys	Phe	Glu	Ala	Pro	Gly	Arg
					35			40					45		

Val	Thr	Arg	Tyr	Leu	Ser	Ser	Gln	Arg	Leu	Ile	Lys	Glu	Ala	Cys	Asp
					50			55			60				

Glu	Ser	Arg	Phe	Asp	Lys	Asn	Leu	Ser	Gln	Ala	Leu	Lys	Phe	Val	Arg
					65			70			75		80		

Asp	Phe	Ala	Gly	Asp	Gly	Leu	Phe	Thr	Ser	Trp	Thr	His	Glu	Lys	Asn
						85			90			95			

Trp	Lys	Lys	Ala	His	Asn	Ile	Leu	Leu	Pro	Ser	Phe	Ser	Gln	Gln	Ala
						100			105			110			

Met	Lys	Gly	Tyr	His	Ala	Met	Met	Val	Asp	Ile	Ala	Val	Gln	Leu	Val
						115			120			125			

Gln	Lys	Trp	Glu	Arg	Leu	Asn	Ala	Asp	Glu	His	Ile	Glu	Val	Pro	Glu
					130			135			140				

Asp	Met	Thr	Arg	Leu	Thr	Leu	Asp	Thr	Ile	Gly	Leu	Cys	Gly	Phe	Asn
						145			150			155		160	

Tyr	Arg	Phe	Asn	Ser	Phe	Tyr	Arg	Asp	Gln	Pro	His	Pro	Phe	Ile	Thr
					165				170			175			

Ser	Met	Val	Arg	Ala	Leu	Asp	Glu	Ala	Met	Asn	Lys	Leu	Gln	Arg	Ala
						180			185			190			

Asn	Pro	Asp	Asp	Pro	Ala	Tyr	Asp	Glu	Asn	Lys	Arg	Gln	Phe	Gln	Glu
						195			200			205			

Asp	Ile	Lys	Val	Met	Asn	Asp	Leu	Val	Asp	Lys	Ile	Ile	Ala	Asp	Arg
					210			215			220				

Lys	Ala	Ser	Gly	Glu	Gln	Ser	Asp	Asp	Leu	Leu	Thr	His	Met	Leu	Asn
					225				230			235		240	

Gly	Lys	Asp	Pro	Glu	Thr	Gly	Glu	Pro	Leu	Asp	Asp	Glu	Asn	Ile	Arg
					245				250			255			

Tyr Gln Ile Ile Thr Phe Leu Ile Ala Gly His Glu Thr Thr Ser Gly  
 260 265 270  
 Leu Leu Ser Phe Ala Leu Tyr Phe Leu Val Lys Asn Pro His Val Leu  
 275 280 285  
 Gln Lys Ala Ala Glu Glu Ala Ala Arg Val Leu Val Asp Pro Val Pro  
 290 295 300  
 Ser Tyr Lys Gln Val Lys Gln Leu Lys Tyr Val Gly Met Val Leu Asn  
 305 310 315 320  
 Glu Ala Leu Arg Leu Trp Pro Thr Ala Pro Ala Phe Ser Leu Tyr Ala  
 325 330 335  
 Lys Glu Asp Thr Val Leu Gly Gly Glu Tyr Pro Leu Glu Lys Gly Asp  
 340 345 350  
 Glu Leu Met Val Leu Ile Pro Gln Leu His Arg Asp Lys Thr Ile Trp  
 355 360 365  
 Gly Asp Asp Val Glu Glu Phe Arg Pro Glu Arg Phe Glu Asn Pro Ser  
 370 375 380  
 Ala Ile Pro Gln His Ala Phe Lys Pro Phe Gly Asn Gly Gln Arg Ala  
 385 390 395 400  
 Cys Ile Gly Gln Gln Phe Ala Leu His Glu Ala Thr Leu Val Leu Gly  
 405 410 415  
 Met Met Leu Lys His Phe Asp Phe Glu Asp His Thr Asn Tyr Glu Leu  
 420 425 430  
 Asp Ile Lys Glu Thr Leu Thr Leu Lys Pro Glu Gly Phe Val Val Lys  
 435 440 445  
 Ala Lys Ser Lys Lys Ile Pro Leu Gly Gly Ile Pro Ser Pro Ser Thr  
 450 455 460  
 Glu Gln Ser Ala Lys Lys Val Arg Lys Lys Ala Glu Asn Ala His Asn  
 465 470 475 480  
 Thr Pro Leu Leu Val Leu Tyr Gly Ser Asn Met Gly Thr Ala Glu Gly  
 485 490 495  
 Thr Ala Arg Asp Leu Ala Asp Ile Ala Met Ser Lys Gly Phe Ala Pro  
 500 505 510  
 Gln Val Ala Thr Leu Asp Ser His Ala Gly Asn Leu Pro Arg Glu Gly  
 515 520 525  
 Ala Val Leu Ile Val Thr Ala Ser Tyr Asn Gly His Pro Pro Asp Asn  
 530 535 540  
 Ala Lys Gln Phe Val Asp Trp Leu Asp Gln Ala Ser Ala Asp Glu Val  
 545 550 555 560  
 Lys Gly Val Arg Tyr Ser Val Phe Gly Cys Gly Asp Lys Asn Trp Ala  
 565 570 575

Thr Thr Tyr Gln Lys Val Pro Ala Phe Ile Asp Glu Thr Leu Ala Ala  
580 585 590

Lys Gly Ala Glu Asn Ile Ala Asp Arg Gly Glu Ala Asp Ala Ser Asp  
595 600 605

Asp Phe Glu Gly Thr Tyr Glu Glu Trp Arg Glu His Met Trp Ser Asp  
610 615 620

Val Ala Ala Tyr Phe Asn Leu Asp Ile Glu Asn Ser Glu Asp Asn Lys  
625 630 635 640

Ser Thr Leu Ser Leu Gln Phe Val Asp Ser Ala Ala Asp Met Pro Leu  
645 650 655

Ala Lys Met His Gly Ala Phe Ser Thr Asn Val Val Ala Ser Lys Glu  
660 665 670

Leu Gln Gln Pro Gly Ser Ala Arg Ser Thr Arg His Leu Glu Ile Glu  
675 680 685

Leu Pro Lys Glu Ala Ser Tyr Gln Glu Gly Asp His Leu Gly Val Ile  
690 695 700

Pro Arg Asn Tyr Glu Gly Ile Val Asn Arg Val Thr Ala Arg Phe Gly  
705 710 715 720

Leu Asp Ala Ser Gln Gln Ile Arg Leu Glu Ala Glu Glu Lys Leu  
725 730 735

Ala His Leu Pro Leu Ala Lys Thr Val Ser Val Glu Glu Leu Leu Gln  
740 745 750

Tyr Val Glu Leu Gln Asp Pro Val Thr Arg Thr Gln Leu Arg Ala Met  
755 760 765

Ala Ala Lys Thr Val Cys Pro Pro His Lys Val Glu Leu Glu Ala Leu  
770 775 780

Leu Glu Lys Gln Ala Tyr Lys Glu Gln Val Leu Ala Lys Arg Leu Thr  
785 790 795 800

Met Leu Glu Leu Leu Glu Lys Tyr Pro Ala Cys Glu Met Lys Phe Ser  
805 810 815

Glu Phe Ile Ala Leu Leu Pro Ser Ile Arg Pro Arg Tyr Tyr Ser Ile  
820 825 830

Ser Ser Ser Pro Arg Val Asp Glu Lys Gln Ala Ser Ile Thr Val Ser  
835 840 845

Val Val Ser Gly Glu Ala Trp Ser Gly Tyr Gly Glu Tyr Lys Gly Ile  
850 855 860

Ala Ser Asn Tyr Leu Ala Glu Leu Gln Glu Gly Asp Thr Ile Thr Cys  
865 870 875 880

Phe Ile Ser Thr Pro Gln Ser Glu Phe Thr Leu Pro Lys Asp Pro Glu

885

890

895

Thr Pro Leu Ile Met Val Gly Pro Gly Thr Gly Val Ala Pro Phe Arg  
900 905 910

Gly Phe Val Gln Ala Arg Lys Gln Leu Lys Glu Gln Gly Gln Ser Leu  
915 920 925

Gly Glu Ala His Leu Tyr Phe Gly Cys Arg Ser Pro His Glu Asp Tyr  
930 935 940

Leu Tyr Gln Glu Glu Leu Glu Asn Ala Gln Ser Glu Gly Ile Ile Thr  
945 950 955 960

Leu His Thr Ala Phe Ser Arg Met Pro Asn Gln Pro Lys Thr Tyr Val  
965 970 975

Gln His Val Met Glu Gln Asp Gly Lys Lys Leu Ile Glu Leu Leu Asp  
980 985 990

Gln Gly Ala His Phe Tyr Ile Cys Gly Asp Gly Ser Gln Met Ala Pro  
995 1000 1005

Ala Val Glu Ala Thr Leu Met Lys Ser Tyr Ala Asp Val His Gln Val  
1010 1015 1020

Ser Glu Ala Asp Ala Arg Leu Trp Leu Gln Gln Leu Glu Glu Lys Gly  
1025 1030 1035 1040

Arg Tyr Ala Lys Asp Val Trp Ala Gly  
1045